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EXAMINER	
KOLKER, DANIEL E	
ART UNIT	**PAPER NUMBER**
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/777,792	SCHENK, DALE B.	
	Examiner	Art Unit	
	DANIEL KOLKER	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-143* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-143* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/29/08, 9/3/08 (5 IDS), 10/21/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The remarks and amendments filed 3 September 2008 have been entered. Claims 119 – 143 are pending and under examination.

Withdrawn Rejections and Objections

2. The following rejections and objections set forth in the previous office action are withdrawn:

A. The objection to the specification is withdrawn in light of the amendment of paragraph [0126] filed 3 September 2008 which deletes the new matter.

B. The rejection under 35 USC 112, first paragraph, for recitation of new matter is withdrawn in light of the amendments which cancel the new matter.

C. The rejection under 35 USC 102(e) as anticipated by Arumugham is withdrawn in light of the amendments. As described in detail below, all claims are now entitled to an effective filing date which precedes that of Arumugham. Thus the reference by Arumugham is not prior art over any pending claim.

D. The provisional non-statutory double-patenting rejection over 10/583503 is withdrawn in light of the arguments. Applicant persuasively argues that the two applications do not have a common inventor or assignee. Applicant stated that the '503 application is assigned to Elan Pharmaceuticals Inc. and Wyeth (remarks, p. 10), and stated that Elan Pharmaceuticals Inc. is under an obligation to assign to Elan Pharma International Ltd., which is the assignee in the present case. If such an obligation in the '503 case were to be carried out in the future, there would at that point be a common assignee between the two applications. If the claims still conflicted, a provisional non-statutory rejection may be made at that point.

E. The examiner's concerns on inventorship (paragraph 14 of the office action mailed 3 April 2008) are currently moot. As stated in the preceding paragraph, the two applications are not currently commonly assigned. However if they were commonly assigned in the future, the concerns may be reiterated in order to clarify actual inventors.

Maintained Rejections and Objections

Priority

3. In the previous office action, the examiner indicated that claims which recited "CRM-197" were not entitled to the benefit of priority, as that specific limitation was not present in any of the

previously-filed applications. Such language has been canceled from all claims which recited it. As such, all pending claims are now entitled to the benefit of priority of application 09/580018 (now U.S. Patent 6,761,888). The effective filing date of all pending claims is 26 May 2000, the date that the '018 application was filed. Support the invention now claimed can be found at column 11 line 1 (residues 1 – 7 of Aβ are a preferred fragment for immunizing), column 20 lines 12 – 21 (peptide immunogens are to be cross-linked to diphtheria toxoid), and column 28 line 12 – 20 (QS-21 is a preferred adjuvant) of the '888 patent. The examiner notes that applicant did not traverse the examiner's determination that claims which do not recite CRM-197 (for example claim 119, as presented in the filing of 30 October 2007) are entitled to 26 May 2000 as the appropriate effective filing date.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 119, 121 – 125, and 131 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Selkoe (U.S. Patent 5,262,332, of record), Wong (1985. Proc. Natl. Acad. Sci. USA 82:8729-8732, of record) and Penney (U.S. Patent 5,773,007, of record).

This rejection stands for the reasons previously made of record and explained in further detail herein. Briefly, Selkoe teaches methods of making antibodies to Aβ protein that are to be used for detection and points to using fragments of Aβ protein "about 8" amino acids long, which is on point to claim 119, which is a product comprising residues 1-7 of Aβ protein linked to a

carrier. However Selkoe does not teach linking the fragment of the Aβ protein to a toxoid from a pathogenic bacterium as recited in claims 119 and 131.

Wong teaches conjugates for production of antibodies against Aβ. Specifically, Wong teaches a conjugate (called OP1) comprising residues 1 – 10 of Aβ conjugated to keyhole limpet hemocyanin (p. 8729 second column third complete paragraph – p. 8730 first column), which is an antigen that can increase the immune system's reaction to the molecule to which it is conjugated. Wong teaches that the antibodies raised against this conjugate are useful for detection of Aβ and diagnosis of Alzheimer's disease. However Wong does not teach residues 1 – 7 of Aβ linked to a carrier which is a toxoid from a pathogenic bacterium as recited in claims 119 and 131.

Penney teaches that purified antigens are often not effective in eliciting an antibody response, and so to boost the response one should include an immunostimulant, such as diphtheria toxoid, encompassed by claims 119 and 131 (see column 1 line 63 – column 2 line 8). Penney teaches that any carrier molecule can be used, including Keyhole Limpet Hemocyanin and any of several toxoids from pathogenic bacteria, including but not limited to diphtheria (see column 5 first paragraph). Penney teaches covalent linkage, as encompassed by claim 125. Penney teaches that adjuvants can optionally be added to antibody-inducing compositions in order to mitigate any local hypersensitivity to the carrier (column 2 lines 7 – 15), which is on point to claim 131, part (b). However Penney does not teach conjugates comprising residues 1 – 7 of Aβ as encompassed by claims 119 and 131.

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to make a composition comprising residues 1 – 7 of Aβ peptide linked to diphtheria toxoid, with a reasonable expectation of success. The motivation to do so would be to stimulate the host animal's immune system to make more antibodies, which could then be used in the diagnostic assays of either Selkoe or Wong. Selkoe teaches that "about 8" amino acids should be used in raising antibodies, and Wong points to the N-terminus of the Aβ protein as that region which is suitable for making antibodies to be used in diagnostic assays. Wong teaches that residues 1 – 10 of Aβ are to be coupled to a heterologous protein for the purpose of increasing antigenicity, so it would have been obvious to one of ordinary skill in the art to couple the shorter peptide (i.e., residues 1 – 7 of Aβ peptide) to a heterologous protein to increase antigenicity. Combining these teachings would have been obvious to one of ordinary skill in the art as both Selkoe and Wong teach making antibodies with these short peptides. Furthermore

Penney teaches that diphtheria toxoid can be substituted for KLH as a heterologous peptide used to increase antigenicity. Thus it would be reasonable to expect success.

Applicant argues, on pp. 7 – 8 of the remarks filed 3 September 2008, that it would not have been obvious to one of ordinary skill in the art to make the composition of claims 119, 121 – 125, and 131 given the teachings of Selkoe, Wong, and Penney. Applicant makes the following points, each of which will be addressed in turn:

1) Since Wong was already using KLH as a carrier, which is suitable for animal administration, there would have been no motivation to select a diphtheria toxoid, which is more suitable for human administration.

2) There would have been no motivation to select residues 1-7 of Aβ protein, and the examiner is using impermissible hindsight reconstruction.

3) There is no reason to select Wong's antibody, which was raised against residues 1 - 10 of Aβ protein rather than any other antibody known at the time the present invention was made.

4) Selkoe does not teach replacing Wong's antibody with one that binds to residues 1-7 of Aβ protein. According to applicant, Selkoe sets 8 amino acid residues as the minimum number to be used when administering the protein to an animal in order to generate an antibody.

Applicant's arguments have been fully considered but they are not persuasive. With respect to 1) above, the selection of a particular known carrier protein from among several disclosed in the prior art would have been obvious to one of ordinary skill in the art. While it is true that both Wong and Selkoe teach making antibodies in mice, which might suggest that KLH would be the most appropriate carrier, non-preferred embodiments (such as diphtheria toxoids as taught at column 2 lines 1 – 10 of Penney) would also be suitable and are to be considered when making determinations of obviousness; see MPEP § 2123(I). Furthermore selection from a finite number of possible carriers, including the diphtheria toxoids disclosed by Penney as being suitable for use in raising antibodies, can be considered obvious. See MPEP § 2143, particularly the section entitled "Exemplary Rationales" and subsection E therein. In the present case, the art (Penney) discloses a finite number of carriers which could be substituted for KLH that was used by Wong. Therefore selection of one of these several would have been obvious to one of ordinary skill in the art.

With respect to 2), applicant states that the examiner is using hindsight reconstruction in an impermissible fashion. The examiner disagrees. While applicant may well have determined that antibodies raised against the claimed composition have certain properties, an artisan of ordinary skill would nonetheless have been motivated to make the composition now claimed. By using on the first 7 residues, as suggested by Selkoe (note Selkoe teaches using "about 8", which includes 7, and specifically points to the N-terminal portion of Aβ protein as suitable), rather than the first 10 residues as taught by Wong, the artisan of ordinary skill would be able to save money, as fewer starting materials would need to be purchased when making a 7 amino acid protein than a 10 amino acid protein. Thus selection of 7 (or put another way "about 8") amino acids from the beginning of the Aβ protein sequence would have been obvious to one of ordinary skill in the art.

With respect to 3), applicant appears to be arguing that there is nothing particularly special about Wong's antibody, and that the artisan of ordinary skill would have had no particular reason to optimize the starting materials used to generate this antibody as opposed to any other known antibody against Aβ protein. The examiner respectfully disagrees. The motivation to select modify the starting materials used to make this antibody would be to make more of it in a cost-efficient manner. Thus the artisan of ordinary skill would be motivated to select optimize the composition comprising residues 1-10 of Aβ conjugated to KLH, which was taught by Wong. The artisan of ordinary skill would reasonably expect that antibodies raised against the optimized composition (i.e., residues 1 – 7 of Aβ conjugated to diphtheria toxoid) would be expected to be useful in the detection assays of Wong.

With respect to 4), applicant states that a "fair reading of Selkoe's comment that a fragment of about 8 or more residues can be used for generating antibodies is that a fragment of 8 residues is about the minimum size and that if a smaller fragment is used there is at least a risk of failure." (remarks, p. 8, emphasis added) The examiner agrees; this is precisely the point. "About 8" is the minimum size suitable for generating antibodies. Clearly 8 is not the absolute minimum, about 8 is. Given the guidance given by Selkoe, namely that there is a degree of latitude around 8, and that 8 should not be considered an absolute minimum size for use in raising antibodies, it would be reasonable to expect success in generating antibodies with 7 rather than exactly 8 amino acids. Furthermore, the reference by Wong provides the artisan of ordinary skill with guidance to attach a carrier protein in order to stimulate the immune system to produce more antibodies. Given that Penney teaches that both KLH taught by Wong and

diphtheria toxoids recited in the claims are suitable as carriers, selection of either of these would have been obvious when choosing the appropriate carrier to attach to the about-8-amino-acid fragment taught by Selkoe.

For at least the reasons above, the rejection is maintained.

5. Claims 119 – 125 and 131 - 132 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Selkoe, Wong, and Penney as applied to claims 119, 121 – 125, and 131 above, and further in view of Restifo (U.S. Patent 5,733,548, of record).

The reasons why claims 119, 121 – 125, and 131 are obvious over Selkoe, Wong, and Penney are set forth above. However none of the references explicitly teaches a plurality of additional copies of the relevant antigen.

Restifo discloses that multiple copies of a peptide can be included in order to increase the immunogenicity of said peptide, and that this method should be effective even in those cases where a single copy of the peptide itself is not antigenic (see column 4 lines 32-36 and column 5 lines 15-22). Thus the reference is on point to claims 120 and 132. However Restifo does not teach comprising residues 1 – 7 of Aβ as encompassed by claims 119 and 131.

It would have been obvious to one of ordinary skill in the art to include multiple copies of the antigen, as suggested by Restifo, with a reasonable expectation of success. The motivation to do so would be to increase the immune response to the peptide antigen. Applicant did not traverse the examiner's determination that the specific limitations of claims 120 and 132 would have been obvious over Restifo. Applicant did not traverse this rejection beyond the reasons and arguments offered for the non-obvious nature of the independent claims. As set forth in the previous rejection, those arguments are not persuasive. Thus claims 120 and 132 stand rejected for the reasons previously made of record.

6. Claims 119, 121 – 125, 131, and 133 – 138 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Selkoe, Wong, and Penney as applied to claims 119, 121 – 125, and 131 above, and further in view of Hancock (U.S. Patent 5,723,130, issued 3 March 1998).

The reasons why claims 119, 121 – 125, and 131 are obvious over Selkoe, Wong, and Penney are set forth above. Note that Selkoe teaches the doses recited in claims 134 – 137 and chemical cross-linking as recited in claim 138. Penney teaches that adjuvants can be

added to the compositions. However none of Selkoe, Wong, or Penney teaches the specific adjuvant QS-21 as recited in claim 133.

Hancock teaches QS-21 (recited in claim 133) is particularly suitable as an adjuvant as it increases the immune response, resulting in more antibodies that tightly bind to the antigen administered (see column 2 lines 25 – 35 for example). However Hancock does not teach comprising residues 1 – 7 of Aβ as encompassed by claims 119 and 131.

It would have been obvious to one of ordinary skill in the art to select QS-21 taught by Hancock as the adjuvant to be included in the compositions rendered obvious by Selkoe in view of Wong and Penney, with a reasonable expectation of success. The motivation to do so would be to select an adjuvant known to be particularly effective in eliciting antibodies, which could then be used in the methods taught by Selkoe and by Wong.

Applicant argues, on pp. 9 – 10 of the remarks filed 3 September 2008, that selection of QS-21 would not have been obvious to one of ordinary skill in the art. Applicant argues that the artisan of ordinary skill would not have had an expectation of success, since the reference by Hancock is on point to immunizing with a foreign antigen (RSV) and the finding that QS-21 increases immune response could not reasonably be extended to those circumstances when a fragment of a native protein (Aβ 1-7) is used rather than a foreign antigen. Additionally, according to applicant, there would have been no motivation to select any adjuvant other than Freund's adjuvant, used by Wong. According to applicant, since there is no teaching as to the superior nature of QS-21 as compared to Freund's, the artisan of ordinary skill would have had no reason to select this adjuvant.

Applicant's arguments have been fully considered but they are not persuasive. Applicant has argued that there would have been no expectation of success, but has not presented any evidence that an expectation of success would have been anything other than reasonable. Attorney's arguments cannot take the place of evidence in those situations when evidence is required (see MPEP § 2145(I)), for example to demonstrate that the expectation of success provided by Hancock is unreasonable. Hancock explicitly states that QS-21 is a known adjuvant to increase the response of the immune system. Even if the examiner were to concede that QS-21 is not the most optimal of all possible adjuvants known in the prior art, this rejection would nonetheless be maintained as non-preferred embodiments constitute prior art and are properly relied upon in determinations of obviousness. Additionally, since QS-21 was known at the time the invention was made to be suitable as an adjuvant, it would have been

obvious to substitute this adjuvant for the adjuvant disclosed in the other references (Freund's adjuvant as disclosed by Selkoe); see MPEP § 2144.06, particularly subsection II entitled "Substituting Equivalents Known for the Same Purpose".

7. Claims 119, 121 – 131, and 133 – 143 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Selkoe, Wong, Penney, and Hancock as applied to claims 119, 121 – 125, 131, and 133 – 138 above, and further in view of Collier (U.S. Patent 5,601,827).

The reasons why claims 119, 121 – 125, 131, and 133 – 138 would have been obvious to one of ordinary skill in the art are set forth above. However none of the references cited explicitly teaches fusion proteins comprising Aβ or fragments thereof as recited in claims 128 and 141, or the specific N- and C-terminal linkages recited in claims 126 - 127, 129 - 130, 139 - 140, and 142 - 143.

Collier teaches vectors for production of diphtheria toxoids (see column 1 final paragraph) and teaches that the vectors can be used for construction of fusion proteins between a diphtheria toxoid and an antigen (see column 4 final paragraph and column 9 final paragraph). The reference is thus on point to fusion proteins, as recited in claims 128 and 141. Collier teaches that construction of vectors for fusion proteins is well-known in the art, but does not explicitly teach the specific N- and C-terminal linkages recited in claims 126 - 127, 129 - 130, 139 - 140, and 142 - 143.

It would have been obvious to one of ordinary skill in the art to use the vectors from Collier to make fusion proteins between Aβ 1-7 and diphtheria toxoid, as rendered obvious by Selkoe in view of Wong, Penney, and Hancock. Collier teaches that the fusion protein method is particularly useful to produce those proteins which will be administered for production of antibodies, so it would be reasonable to expect success in using such methodology. Additionally, as Collier teaches that fusion proteins are generally known in the art, and re-arrangement of parts is generally not considered a patentable contribution (see MPEP § 2144.04(VI)), selection of either the N- or C-terminus of the Aβ fragment would have been obvious. Applicant did not traverse the examiner's determination that the specific limitations recited in claims 126 – 127, 129 – 130, 139 – 140, and 142 – 143 would have been obvious in view of Collier, beyond the reasons set forth for other rejections. As the examiner has determined that the claimed invention of those parent claims is obvious, and applicant did not traverse the examiner's determination that fusion proteins and specific linkage orientations

would have been obvious to one of ordinary skill in the art, this rejection stands for the reasons previously made of record.

Conclusion

8. No claim is allowed.

9. The art made of record and not relied upon is considered pertinent to applicant's disclosure. U.S. Patent Application Publication 2008/0145373. The reference is the publication of application 11/841919, which is a division of 10/583503 discussed in paragraphs numbered 2D and 2E above. The application is assigned to Elan Pharmaceuticals, Inc. and Wyeth. However as set forth in paragraph 2D above, Elan Pharmaceuticals, Inc. is not the same assignee as that of the present case.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANIEL KOLKER whose telephone number is (571)272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel E. Kolker/
Primary Examiner, Art Unit 1649
November 14, 2008